## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Are noise and air pollution related to the incidence of dementia? A cohort study in London, England |
| **AUTHORS** | Carey, Iain; Anderson, H; Atkinson, Richard; Beevers, Sean; Cook, Derek; Strachan, David; Dajnak, David; Gulliver, John; Kelly, Frank |

## VERSION 1 – REVIEW

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| **REVIEWER** | Jun Wu<br>University of California, Irvine, USA |
| **REVIEW RETURNED** | 10-Mar-2018 |

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| **GENERAL COMMENTS** | This retrospective study investigated the association between environmental exposures (i.e. air pollution and noise) and the incidence of dementia in London. The study used primary care data of over 130k records. Air pollution exposures to NO2, PM2.5 and O3 were estimated using a dispersion model. Roadway noise was estimated using a traffic noise exposure model. Hazard ratios were estimated using Cox models. The authors concluded that they have found evidence of a positive association between residential levels of air pollution and dementia.<br><br>The paper was in general well written, but I have several major concerns below:<br>1. Average annual concentrations in 2004 were estimated for the three air pollutants NO2, PM2.5 and O3. It looks like a snapshot of exposure estimates that only captured spatial variability. No longitudinal or temporal data were available. The authors did not mention whether they have residential address history and if they were able to predict cumulative exposures during the study period. They acknowledged in the Discussion section that they were not able to obtain residential addresses before 2005. The lack of addresses before 2005 and addresses during the study period is one of the major weaknesses of the study.<br>2. Although the dispersion model simulated pollutant concentrations at a resolution of 20 m * 20 m, it does not mean that the model can reliably predict spatial variations of air pollutants at this resolution. The authors need to discuss the limitations and uncertainties of the dispersion modeling approach.<br>3. Dispersion model was used to predict O3 concentration. The authors mentioned that “It incorporates hourly meteorological measurements, empirically derived concentrations of NO-NO2-O3 and derived PM (particulate matter)…” I wonder how this NO-NO2-O3 relationship was applied and how accurate the NO2 and O3 estimates were.<br>4. What are the correlations of the three air pollutants (NO2, PM2.5, and O3)? Are air pollutants highly correlated with noise? Such information will be helpful to better understand the exposure |

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| | estimates.<br>5. The noise model considered traffic flows and speeds, road geography, land cover, and building heights. Did the model take into account types of vehicles, sound-walls/trees, and other types of emission sources (e.g. railway)? Did the model incorporate traffic diurnal patterns?<br>6. Is there any biological hypothesis about the differences between Alzheimer's disease and vascular dementia?<br>7. The authors stated that "…the reality was that subtle roadside changes predicted by the model were small in comparison to larger differences estimated between the areas represented by the GP practices, suggesting most modelled variation was between (practice) areas." I cannot find data that support this statement. They need to show the supporting data in the supplemental materials.<br>8. The authors mentioned that "patients residing in the top quintile of NO2 (>41.5 µg/m3) had a marked increase in risk (HR=1.58, 95% CI 1.24-2.01) compared to those in the bottom quintile (<31.9 µg/m3)." But results in Table 4 did not show the sameexact results. Did the author refer to the results in Figure 1? Were Table 4 and Figure 1 results the same? |

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| **REVIEWER** | Giulia Cesaroni<br>Department of Epidemiology, Regional Health Service, Rome, Italy |
| **REVIEW RETURNED** | 19-Mar-2018 |

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| **GENERAL COMMENTS** | GENERAL COMMENTS<br>This study evaluates the association between air pollution and noise exposure at residence and incidence of dementia in a cohort of 140,000 subjects across Greater London. It certainly adds to the limited available body of evidence on this association. The work has several strengths; the cohort is rich of individual risk factors such as smoking, BMI, and alcohol consumption. The manuscript is well written, and it is a pleasure to read it.<br>I have the following main comments:<br><br>SPECIFIC COMMENTS<br>1. To my opinion, IHD, stroke, diabetes and heart failure are more mediators than confounders in the association between air pollution and dementia. Hence, in table 3, I would perform the HR4 and HR5 as HR2 plus additional adjustment for pollutants and noise. I suggest exploring a possible mediating effect.<br>2. In Table 1, I would add BMI, alcohol consumption, and the variables used for stratification (years of registration (<10 and 10+), inner/outer London practice) with a measure of air pollution, such as NO2. This would help the reader to better understand the distribution of exposure in the population<br>3. The results on vascular dementia (Table 4), but also the results on subjects with IHD, stroke, diabetes, etc. (Figure 2) are unexpected. I suggest performing as additional analysis a competing risk analysis with death as competing event.<br><br>MINOR COMMENTS<br>1. In your data, does sex follows the proportional hazards assumption?<br>2. I suggest to add p for interaction in Figure 2 |

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| **REVIEWER** | Zorana Jovanovic Andersen<br>Department of Public Health, University of Copenhagen<br>Copenhagen, Denmark |

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| **REVIEW RETURNED** | 26-Mar-2018 |

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| **GENERAL COMMENTS** | In article 'Noise and air pollution and the incidence of dementia: a cohort study in London,' authors study association between long-term exposure to air pollution and road traffic noise and incidence of dementia, in a large cohort of 130,978 adults from London, 50-79 years of age, registered with their general practitioner on 1.1.2005, and followed for dementia incidence (in dementia-free subjects) until 2011. 1,527 (1.2%) of subjects developed dementia during follow-up (2005-2011) according to the Clinical Practice Research Datalink (CPRD), primary care database, of whom 35% received diagnosis Alzheimer's disease (AD) and 29% vascular dementia, while majority (39%) of dementia cases were of unknown subtype. Exposure to PM2.5, NO2, and O3 were estimated in 2004 by KCLurban dispersion models at a resolution 20mx20m. Road traffic noise at night (Lnight) was modeled by TRANEX model at postal code level. Authors used Cox PH model with a shared frailty/random effect at GP level, adjusting for age, sex, ethnicity, smoking, alcohol consumption, BMI, and co-morbidity. Authors detected strong positive association between NO2 and PM2.5 and incidence of dementia that seemed strongest with NO2, and limited to AD, and robust to adjustment for Lnight. Weak association with rad traffic noise diminished after adjustment for NO2. This is a very well designed and written paper, which presents novel and important results on association between air pollution, noise and dementia incidence. Major strength of the study is availability of data on air pollution and road traffic noise simultaneously, as well as large sample size of population of London. Weakness of the approach is definition of dementia based on GP records (which is novel definition as compared to earlier studies on the topic), which needs to be addressed in more detail. More detail on choice for focusing on air pollution data from 2004, and not using entire exposure history during follow-up 2005-2011, is needed, and preferably supported by additional analyses/resuts/Tables. Some more detail on study population selection and data structure is needed, prefreably with a Map of study population. Finally, lack of some possibly relevant confounders at the individual levels (education, income, occupation) needs to be acknolwedged. Paper is methodologically of high quality, very well written, and contributes with novel data and results, but needs to address several points before it can be accepted for publication.<br><br>Specific comments:<br>My major concern is accuracy, validity and completeness of primary care diagnosis of dementia. Here I have several comments:<br>1. In Methods, Data Source, page 4 and 5, authors state that three quarters of primary care practices in UK consented their data to CPRD. Is there any knowledge whether these three quarters are selected somehow, by socio-economic status/location, in some way that could be associated with air pollution/noise? Furthermore, authors state on page 5 that they have selected 75 practices that lay within the study area bound by M25 motorway around Greater London. Are these 75 practices the total of all of available (of the three quarters of those who agreed to participate in CPRD) in the above-mentioned London area, or a subset of these? If this is a subset, how many were there in total? How many people were in average linked to a single primary care practice? All in all, a better explanation (flow-chart) of selection of practices/study population that contributed with the data in this paper and even a map of these and their placement in London, with practices and air pollution and |

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| | noise levels, would be very useful for better understanding of selection and location of study population.<br>2. What is the coverage of dementia definition presented in the paper? Authors do mention that under recording is an issue, and that presented rates are likely underestimated. However, it would be nice with some quantification of these statements. Are prevalence (391 cases in 2005) and incidence of dementia comparable to that for the rest of UK/London in this period? Can authors calculate and present prevalence and incidence rates of dementia in their population and discuss how these compare to official statistics? Related to this, in Table 1, person-years and incidence rates should presented, as these are preferred descriptive statistic to % of person with incident dementia.<br>3. Distribution of subtypes of dementia is strange (35% AD and 29% vascular dementia), where one would expect majority of dementia to be AD (50-70%) and 15-20% vascular dementia. If vascular dementia is correctly diagnosed, the majority of non-specified dementia would be expected to be AD. Yet, results are rather inconsistent in three groups, suggesting strongest association with diagnised AD. Is there any insight into GP data and why is vacsular dementia overrepresented/or correctly diagnosed, whereas ad seems to be largely underreported? Since vasculaer dementia is often preceded by stroke, and stroke history data would be availabel to GP, this may be the reason for easier dagnosis at GP, whereas AD requires more testing (MRI and PET scanning) at secondary health care. Who are the patients for whom AD diagnoses is made at GP? Mild or more severe AD? This group seems differentially related to air pollution than non-specified dementia, which is important to understand. Some insight would be good here, and perhaps caution in interpreting findings with these subtypes, due to skewed distribution and questionable accuracy of these data.<br>4. My other concern is that earlier publication with these primary care data on cardiorespiratory outcomes [reference 16], failed to show associations, although these would be expected, according to existing literature on well-established health effects of air pollution. Authors suggest (on page 18, Discussion, line5-7) that 'geographical pattern specific to dementia and potentially AD, could be explanation for this', but they do not provide any reference/evidence of this. Again, a map of the study area and pollution levels, would be nice for some of these discussions and better understanding of what study population we have in this study, and how it may differ from rest of London/UK, and how geographical patterns in dementia may differ from those in cardiorespiratory disease.<br><br>Other comments:<br>5. Estimates of Air and Noise Pollution Exposure (page 5). Authors state that they focused in this analysis on 2004 air pollution values. Why? They mention later (for the first time) in the Discussion on page 16, line 7, that they actually had air pollution levels for other years during the follow-up (2005-2011), and that 'alternative analyses using these made no discernable difference.' What alternative analyses and how exactly were they conducted? Did they try to fit time-varying Cox PH models to use running means of longest possible exposure windows, and explore effect of longer exposures? Authors should have stated in the Methods that air pollution data were available for entire follow-up period, and justify better, why they were not used in main analyses, and why 2004 was chosen as main exposure matrix. Also, if authors did run analyses for air pollution data during follow-up period (as it would be expected given that these data exist), this should have been presented and |

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| | explained in the Statistical Analyses section, as sensitivity analyses, or part of main analyses, and they should be also mentioned in the results section, and even (preferably) with an additional Table.<br>6. Related to this, it should be stated clearly whether road traffic noise was estimated in 2004, or did authors had data for follow-up years as well?<br>7. Statistical analyses: authors correctly fit a random effect survival (Cox PH) model, to account for shared frailty/correlation for people belonging to the same general practice. However, since air pollution data are estimated at 20mx20m resolution, it seems that there is another level of shared frailty/or clustering (possibly demanding different statistical model, two-level frailyt), of people who are assigned same air pollution levels, which is within general practice area? Or did all subjects have individual air pollution levels assigned? This is not clear completely, and it would be helpful if authors explain this better.<br>8. If understood correctly, it seems that road traffic noise data were modeled at poorer resolution (zip codes) than air pollution data (20mx20m)? Could this then explain weaker association with dementia, due to smaller contrast in exposure, which fail to capture finer, real exposure contrasts in noise exposure at residence? If this is understood correctly, it should be acknowledged in the discussion. Another matter is 'clustering' of people with same noise levels, and how this differs from 'air pollution' and primary physician 'cluster'? At the same time, outcome and confoudern data are available at the individual level. The data structure is somewhat complicated and little difficult to follow at times.<br>9. Please add more detail on the confounder definition in the Methods. Are they collected by GP? BMI is measured or self-reported? In addition, were co-morbidities defined from GP records? Was this done in the same way as in reference 16? On page 6, it is stated that 'Following previous methods', and referring to author's earlier paper: 'we also collated information on ethnicity, smoking, etc..', but it would be nice to have this important information about relevant confounders sources and definition without having to look up earlier paper.<br>10. Lack of information on education, income, occupation, IQ, etc., all of which may be important confounders/risk factors of dementia, is a weakness of this study (especially is there is some selection by socio-economic status) which should be acknowledged up front as one of the major weaknesses.<br>11. Page 15, line 37 what is meant by unusual clustering of their address flag?<br>12. Discussion, page 17, line 24-30, authors refer to study by Oudin et al. but forgot to refer to it. I assume this is referene 37, Oudin et al., pleas einsert it.<br>13. Authors failed to mention study by Kioumourtzoglo et al. large study of 9.8 million Medicare enrollees ≥ 65 years in US dwhich etected association between PM2.5 and first-ever hospitalization for dementia (HR = 1.08; 1.05-1.11) and AD (HR = 1.15; 1.11-1.19) per 1 µg/m,3 in line with current findings:<br>Kioumourtzoglou M-A, Schwartz JD, Weisskopf MG, Melly SJ, Wang Y, Dominici F, et al. 2016. Long-term PM2.5 Exposure and Neurological Hospital Admissions in the Northeastern United States. Environ. Health Perspect. 124:23–9; doi:10.1289/ehp.1408973.<br>14. Study by Wu et al. is from 2015, and not 2017, as stated in the Reference list.<br>https://www.ncbi.nlm.nih.gov/pubmed/27239507 |

**VERSION 1 – AUTHOR RESPONSE**

Reviewers' Comments to Author:

Reviewer: 1

Reviewer Name: Jun Wu

Institution and Country: University of California, Irvine, USA

Competing Interests: None declared.

This retrospective study investigated the association between environmental exposures (i.e. air pollution and noise) and the incidence of dementia in London. The study used primary care data of over 130k records. Air pollution exposures to NO2, PM2.5 and O3 were estimated using a dispersion model. Roadway noise was estimated using a traffic noise exposure model. Hazard ratios were estimated using Cox models. The authors concluded that they have found evidence of a positive association between residential levels of air pollution and dementia.

The paper was in general well written, but I have several major concerns below:

1. Average annual concentrations in 2004 were estimated for the three air pollutants NO2, PM2.5 and O3. It looks like a snapshot of exposure estimates that only captured spatial variability. No longitudinal or temporal data were available. The authors did not mention whether they have residential address history and if they were able to predict cumulative exposures during the study period. They acknowledged in the Discussion section that they were not able to obtain residential addresses before 2005. The lack of addresses before 2005 and addresses during the study period is one of the major weaknesses of the study.

Response: **We did already state in the discussion (page 16, lines 5-6) that we had annual concentrations for all pollutants over the study follow-up (2004-2010), but since these were highly correlated over time (r>0.95), the key differences in exposure between patients were essentially obtained by our single "snapshot" in 2004.**

While we could consider incorporating the exposure measures during follow-up, we think these are less relevant to any potential association with dementia, where the pathogenesis of the disease may have taken place over many years previously.

Response: **Residential address (current or historical) was not available to us, to preserve patient anonymity and allow the study to be carried out. While we had raised the lack of historical address as a weakness (page 15, lines 50-55) we agree we should give this issue more prominence as a major weakness. However, all large epidemiological studies of long-term exposure to pollution in older adults will struggle to estimate cumulative exposure to some degree. We have now revised the discussion accordingly.**

2. Although the dispersion model simulated pollutant concentrations at a resolution of 20 m * 20 m, it does not mean that the model can reliably predict spatial variations of air pollutants at this resolution. The authors need to discuss the limitations and uncertainties of the dispersion modeling approach.

Response: **We accept that there are uncertainties in modelling air pollution at small spatial scales however between 2003 and 2010, a comparison of observed vs. modelled concentrations across all sites in London (up to 100 sites for NOx/NO2 and from suburban background to kerbside) has been created and the spearman correlation coefficient (r) and normalised mean bias (NMB) calculated. These results are available (Table 2) from a comprehensive description of this model which we referenced in the methods (reference 18):**

https://www.kcl.ac.uk/lsm/research/divisions/aes/research/ERG/research-projects/traffic/TRAFFIC-SM-Air-pollution-Model.pdf

**The average values of r for NOX and NO2 are 0.87 and 0.9, respectively. The model performs slightly less well for O3 concentrations but still results in an average r value of 0.85. The value of r for PM2.5 are 0.74. The NMB results for NOX, NO2, O3 and PM2.5 are: -9%, <1%, 3.5% and 16%, respectively. These results against a range of sites represent good model performance even at the small spatial scales needed to predict kerbside concentrations.**

3. Dispersion model was used to predict O3 concentration. The authors mentioned that "It incorporates hourly meteorological measurements, empirically derived concentrations of NO-NO2-O3 and derived PM (particulate matter)…" I wonder how this NO-NO2-O3 relationship was applied and how accurate the NO2 and O3 estimates were.

Response: **The report (reference 18) we mentioned in point 2, provides further details on accuracy.**

**A further description of how the modelling was done can be found in**

**Carslaw DC, Beevers SD and Fuller GW., 2001. An empirical approach for the prediction of annual mean nitrogen dioxide concentrations in London, Atmospheric Environment, 35(8):1505-1515.**

4. What are the correlations of the three air pollutants (NO2, PM2.5, and O3)? Are air pollutants highly correlated with noise? Such information will be helpful to better understand the exposure estimates.

Response: **We think the reviewer may have missed that the correlations were given in the footnote of Table 2, and discussed on page 9 in the results. However, we accept this was not clear and have revised Table 2 to give them more prominence. Correlations between air pollutants and Lnight was moderate, which is consistent with overall findings in a study specifically looking at the spatial relationships of air pollution and noise for the whole of London (Fecht et al. 2016; reference 20 in the manuscript).**

5. The noise model considered traffic flows and speeds, road geography, land cover, and building heights. Did the model take into account types of vehicles, sound-walls/trees, and other types of emission sources (e.g. railway)? Did the model incorporate traffic diurnal patterns?

Response: **The road traffic noise model (TRANEX) is based on the UK standard method (CRTN; Calculation of Road Traffic Noise) and accounts separately for light and heavy vehicles. We included the same traffic flows/speeds and diurnal traffic patterns that were used in the air pollution model. We did not have information on noise barriers and CRTN does not model noise absorption/diffraction from trees (3-D); noise attenuation due to vegetation is accounted for by ground cover (2-D). We did not include information on railway noise, which affects (>50dB) a relatively small proportion of the resident population.**

6. Is there any biological hypothesis about the differences between Alzheimer's disease and vascular dementia?

Response: **We are not entirely clear what is being asked here. Vascular dementia is often a result of a prior acute event such as a stroke or transient ischemic attack, where the blood flow to the brain has been interrupted. The relationship between air pollution and stroke has been hypothesized previously, and shown in some cohort studies e.g. Andersen et al., "Stroke and Long-Term Exposure to Outdoor Air Pollution From Nitrogen Dioxide A Cohort Study." Stroke. 2012;43(2):320-5. By contrast, causes of Alzheimer's disease largely remain a mystery. Therefore, if one observed a relationship with dementia and air pollution, it may be due to associations with prior stroke and specific to vascular dementia. Although we have reservations about the power and specificity of our sub-type analyses, we think it is an interesting observation that, if anything, we see the opposite in the study.**

7. The authors stated that "…the reality was that subtle roadside changes predicted by the model were small in comparison to larger differences estimated between the areas represented by the GP practices, suggesting most modelled variation was between (practice) areas." I cannot find data that support this statement. They need to show the supporting data in the supplemental materials.

Response: **We agree that we failed to provide clear evidence of this. We have revised Table 2 to now include the intra-class correlations for all pollutants. These show that for air pollution most variation is between practice (ICCs>0.7).**

8. The authors mentioned that "patients residing in the top quintile of NO2 (>41.5 μg/m3) had a marked increase in risk (HR=1.58, 95% CI 1.24-2.01) compared to those in the bottom quintile (<31.9 μg/m3)." But results in Table 4 did not show the sameexact results. Did the author refer to the results in Figure 1? Were Table 4 and Figure 1 results the same?

Response: **We think the reviewer has got confused between the analysis in Figure 1 which was based on "Any Dementia" versus Table 4 which sub-divided Dementia into 3 categories – Alzheimer's' Disease, vascular dementia and Non-specific dementia. Thus, the HR=1.58 is for "Any" while the HRs in Table 4 for the same comparison (2.04, 1.12, 1.54) will vary. (Please note these estimates have now changed due to the overall revision in the analysis we carried out – see earlier note to editor).**

**To help with the interpretation here, we have now included a new Supplementary Table S3 which gives the estimates plotted in Figure 1.**

Reviewer: 2

Reviewer Name: Giulia Cesaroni

Institution and Country: Department of Epidemiology, Regional Health Service, Rome, Italy

Competing Interests: None declared

GENERAL COMMENTS

This study evaluates the association between air pollution and noise exposure at residence and incidence of dementia in a cohort of 140,000 subjects across Greater London. It certainly adds to the limited available body of evidence on this association. The work has several strengths; the cohort is rich of individual risk factors such as smoking, BMI, and alcohol consumption. The manuscript is well written, and it is a pleasure to read it.

Response: **Thank you**

I have the following main comments:

SPECIFIC COMMENTS

1. To my opinion, IHD, stroke, diabetes and heart failure are more mediators than confounders in the association between air pollution and dementia. Hence, in table 3, I would perform the HR4 and HR5 as HR2 plus additional adjustment for pollutants and noise. I suggest exploring a possible mediating effect.

Response: **We completely agree with this point. Our intention was to see if these co-morbidities could explain away the finding with dementia, despite the fact that they may indeed be on the disease pathway (i.e. stroke preceding vascular dementia). We have changed HR4 and HR5 as suggested, though the impact is negligible. (Please note that HR5 is now found in Supplementary Table S1).**

2. In Table 1, I would add BMI, alcohol consumption, and the variables used for stratification (years of registration (<10 and 10+), inner/outer London practice) with a measure of air pollution, such as NO2. This would help the reader to better understand the distribution of exposure in the population

Response: **We have added BMI, years of stratification and London borough to the revised Table 1. Note that the revised Table 1 now shows incidence rates (responding to comment #2 from Reviewer 3). We did not add alcohol consumption as we have dropped it from the regressions as it was not a significant predictor and made no impact to the findings. (This may seem**

**surprising, but it may not be reliably recorded and may be a poor marker of past consumption).**

3. The results on vascular dementia (Table 4), but also the results on subjects with IHD, stroke, diabetes, etc. (Figure 2) are unexpected. I suggest performing as additional analysis a competing risk analysis with death as competing event.

Response: **As we have commented elsewhere, we are cautious about the sub-type analyses in Table 4, due to uncertainty around coding, and limited power. We have extended follow-up to 2013 to boost some the number of sub-types recorded, which attenuated some of the estimates/differences but hasn't changed our general conclusions.**

**A competing risk analysis is an intriguing suggestion as almost 8% of the cohort died without dementia during follow-up. We are uncertain how this can be adapted into the frailty Cox model, but have fitted some Fine-Gray competition risks regressions and compared these to non-frailty Cox models. For an IQR change in NO2, the HR for all dementia (HR=1.163) was virtually identical to the sub-hazard ratio from a competing risks regression (SHR=1.161). Therefore, we conclude that competing risks are not an issue in this dataset.**

MINOR COMMENTS

1. In your data, does sex follows the proportional hazards assumption?

Response: **If we generate a time dependent covariate from the interactions of sex and a function of survival time from our main models, none of these time dependent covariates were significant. Therefore there is no evidence suggesting a violation of the proportional hazards assumption.**

2. I suggest to add p for interaction in Figure 2

Response: **We are not entirely convinced this is necessary, as it should be clear that none of the interactions approach statistical significance as the 95%CI's clearly overlap. The main message of the figure is the consistency of the estimate across sub-groups, not that there is any evidence for effect modification. However, we have provided the p-values in a footnote.**

Reviewer: 3

Reviewer Name: Zorana Jovanovic Andersen

Institution and Country: Department of Public Health, University of Copenhagen, Copenhagen, Denmark

Competing Interests: None declared

In article ‘Noise and air pollution and the incidence of dementia: a cohort study in London,’ authors study association between long-term exposure to air pollution and road traffic noise and incidence of dementia, in a large cohort of 130,978 adults from London, 50-79 years of age, registered with their general practitioner on 1.1.2005, and followed for dementia incidence (in dementia-free subjects) until 2011. 1,527 (1.2%) of subjects developed dementia during follow-up (2005-2011) according to the Clinical Practice Research Datalink (CPRD), primary care database, of whom 35% received diagnosis Alzheimer’s disease (AD) and 29% vascular dementia, while majority (39%) of dementia cases were of unknown subtype. Exposure to PM2.5, NO2, and O3 were estimated in 2004 by KCLurban dispersion models at a resolution 20mx20m. Road traffic noise at night (Lnight) was modeled by TRANEX model at postal code level. Authors used Cox PH model with a shared frailty/random effect at GP level, adjusting for age, sex, ethnicity, smoking, alcohol consumption, BMI, and co-morbidity. Authors detected strong positive association between NO2 and PM2.5 and incidence of dementia that seemed strongest with NO2, and limited to AD, and robust to adjustment for Lnight. Weak association with rad traffic noise diminished after adjustment for NO2. This is a very well designed and written paper, which presents novel and important results on association between air pollution, noise and dementia incidence. Major strength of the study is availability of data on air pollution and road traffic noise simultaneously, as well as large sample size of population of London. Weakness of the approach is definition of dementia based on GP records (which is novel definition as compared to earlier studies on the topic), which needs to be addressed in more detail. More detail on choice for focusing on air pollution data from 2004, and not using entire exposure history during follow-up 2005-2011, is needed, and preferably supported by additional analyses/resuts/Tables. Some more detail on study population selection and data structure is needed, prefreably with a Map of study population. Finally, lack of some possibly relevant confounders at the individual levels (education, income, occupation) needs to be acknolwedged. Paper is methodologically of high quality, very well written, and contributes with novel data and results, but needs to address several points before it can be accepted for publication.

Response: **We will address the above points in the specific comments below**

Specific comments:

My major concern is accuracy, validity and completeness of primary care diagnosis of dementia. Here I have several comments:

1. In Methods, Data Source, page 4 and 5, authors state that three quarters of primary care practices in UK consented their data to CPRD. Is there any knowledge whether these three quarters are selected somehow, by socio-economic status/location, in some way that could be associated with air pollution/noise? Furthermore, authors state on page 5 that they have selected 75 practices that lay within the study area bound by M25 motorway around Greater London. Are these 75 practices the total of all of available (of the three quarters of those who agreed to participate in CPRD) in the above-mentioned London area, or a subset of these? If this is a subset, how many were there in total? How many people were in average linked to a single primary care practice? All in all, a better explanation (flow-chart) of selection of practices/study population that contributed with the data in this paper and even a map of these and their placement in London, with practices and air pollution and noise levels, would be very useful for better understanding of selection and location of study population.

Response: **We agree that the completeness of the primary care diagnoses of dementia is a concern and discuss this further in point 2 below. With regards the selection of primary care practices, we accept that we did not provide enough details in the methods and have taken steps to correct it. To answer specific points**

**- In 2004, the mid-year estimate for London was 7.4 million. In our 75 practices, we had 555,385 patients registered on January 1st 2004 – so we estimate that these practices represent about 7% of the Greater London population. We have added this statement to the methods.**

**- An average practice contains about 7,500 patients (all ages) at any time during the 2000s.**

**- We did not select the practices per se, nor have any information regarding their selection. The 75 practices were all the available practices contributing to the computer system (Vision) at that time who had consented for linkage. (About a further 20 were in CPRD but had not consented).**

**- We are not allowed to know the location of the practices to maintain patient anonymity. Thus, we are not convinced a map is of any great benefit on this occasion.**

2. What is the coverage of dementia definition presented in the paper? Authors do mention that under recording is an issue, and that presented rates are likely underestimated. However, it would be nice with some quantification of these statements. Are prevalence (391 cases in 2005) and incidence of dementia comparable to that for the rest of UK/London in this period? Can authors calculate and present prevalence and incidence rates of dementia in their population and discuss how these compare to official statistics? Related to this, in Table 1, person-years and incidence rates should presented, as these are preferred descriptive statistic to % of person with incident dementia.

Response: **We thank the reviewer for a good suggestion. As we stated, we believe under recording of diagnoses to be a problem, such that we only excluded 0.3% of our patients in 2005, based on a pre-existing dementia diagnosis on their record. National figures by age-group suggest prevalence of 1.3% among 65-69 year olds, 2.9% among 70-74 year olds and 5.9% among 75-79 year olds. By contrast in our data, these figures would be 0.3%, 0.6% and 1.4%. However, the prevalence of dementia is likely to be significantly lower in London, where older patients with the disease will move outside the area, in part due to property prices. Regional prevalence estimates were not directly available, but summary maps confirm the low prevalence rates across Greater London**

https://www.dementiastatistics.org/statistics/dementia-maps/

**It should also be noted that we excluded any patients residing in care-homes. Including them would have raised our "exclusion" prevalence to 0.7%, 1.2% and 2.4% in these age-groups.**

**We have now updated Table 1 to included incidence rates.**

3. Distribution of subtypes of dementia is strange (35% AD and 29% vascular dementia), where one would expect majority of dementia to be AD (50-70%) and 15-20% vascular dementia. If vascular dementia is correctly diagnosed, the majority of non-specified dementia would be expected to be AD. Yet, results are rather inconsistent in three groups, suggesting strongest association with diagnised AD. Is there any insight into GP data and why is vacsular dementia overrepresented/or correctly diagnosed, whereas ad seems to be largely underreported? Since vasculaer dementia is often preceded by stroke, and stroke history data would be availabel to GP, this may be the reason for

easier dagnosis at GP, whereas AD requires more testing (MRI and PET scanning) at secondary health care. Who are the patients for whom AD diagnoses is made at GP? Mild or more severe AD? This group seems differentially related to air pollution than non-specified dementia, which is important to understand. Some insight would be good here, and perhaps caution in interpreting findings with these subtypes, due to skewed distribution and questionable accuracy of these data.

Response: **Dementia sub-type will likely only be coded only after the patient has seen a specialist diagnostic service. If the patient has not seen a specialist then they may not get a specific diagnostic code, but just a non-specific one. It is only in more recent years that the Quality and Outcomes Framework has required a whole basket of tests to be done, which will have increased referral rates and therefore increased numbers of more specific diagnoses for dementia. But the reviewer is probably right in saying that vascular dementia is an easier diagnosis to make than Alzheimer's, and this may reflect the patterns in the primary care coding we are seeing.**

**To try and improve sub-type recording we made the following updates: (i) extend follow-up to the end of 2013, (ii) use any mention of vascular dementia or Alzheimer's disease on the death record to classify non-specific cases. This resulted in 39% Alzheimer's, 29% Vascular and 34% Non-specific (or mixed). It may be the distribution of types is different across London. While we agree with reviewer's assertion that the non-specific coding may be more likely to be Alzheimer's, this still appears to be a mixed group based on key characteristics e.g. the % with a prior stroke were: Vascular (15.6%), Non-specific (7.6%), Alzheimer's (4.7%).**

**Ultimately, we agree that caution needs to be applied to these findings, particularly the sub-type. Despite the questionable accuracy of sub-type, we still think the presentation is worthwhile, and has produced findings which require further investigation.**

4. My other concern is that earlier publication with these primary care data on cardiorespiratory outcomes [reference 16], failed to show associations, although these would be expected, according to existing literature on well-established health effects of air pollution. Authors suggest (on page 18, Discussion, line5-7) that 'geographical pattern specific to dementia and potentially AD, could be explanation for this', but they do not provide any reference/evidence of this. Again, a map of the study area and pollution levels, would be nice for some of these discussions and better understanding of what study population we have in this study, and how it may differ from rest of London/UK, and how geographical patterns in dementia may differ from those in cardiorespiratory disease.

Response: **We are not sure that the failure to find associations previously with this data should necessarily invalidate our current findings. The point we were trying to make here is that Dementia may have a different geographical pattern than cardiorespiratory outcomes, which could explain the contrast in two different findings.**

**We accept that we need to cautious in extending these findings nationally across England. Our study population may be slightly more affluent than average (we were under represented in the most deprived fifth category). Of perhaps more concern is the regional variation of the prevalence and diagnosis rates of dementia, which have been reported to vary across England, with Greater London being one of the lowest areas.**

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/262139/Dementia.pdf

**We have now updated the discussion to make this point and include the report as a new reference.**

**As explained in point 1, we are unable to provide any specific geographical information in order to preserve patient anonymity.**

Other comments:

5. Estimates of Air and Noise Pollution Exposure (page 5). Authors state that they focused in this analysis on 2004 air pollution values. Why? They mention later (for the first time) in the Discussion on page 16, line 7, that they actually had air pollution levels for other years during the follow-up (2005-2011), and that 'alternative analyses using these made no discernable difference.' What alternative analyses and how exactly were they conducted? Did they try to fit time-varying Cox PH models to use running means of longest possible exposure windows, and explore effect of longer exposures? Authors should have stated in the Methods that air pollution data were available for entire follow-up period, and justify better, why they were not used in main analyses, and why 2004 was chosen as main exposure matrix. Also, if authors did run analyses for air pollution data during follow-up period (as it would be expected given that these data exist), this should have been presented and explained in the Statistical Analyses section, as sensitivity analyses, or part of main analyses, and they should be also mentioned in the results section, and even (preferably) with an additional Table.

Response: **We had annual concentrations for all pollutants available to us for the years 2004-2010. However, since we wished to maximize follow-up time and the number of the incident cases available, we choose to focus on modelled exposures in 2004 as this was the earliest available. Since we expect that disease progression may have begun many years before the date of the "incident" diagnosis, we are less convinced about the contribution of post 2004 exposures.**

**Moreover, since all the pollutants are highly correlated over high (r>0.99), results are virtually identical whether the model is based on a different year's exposure, or a time updating exposure. We have added a comment to the text about this, but do not see the value in adding these results to the paper.**

6. Related to this, it should be stated clearly whether road traffic noise was estimated in 2004, or did authors had data for follow-up years as well?

Response: **We used road traffic noise estimated in 2004, but had all years between 2004-2010 available as the other pollutants. We have clarified this in the methods.**

7. Statistical analyses: authors correctly fit a random effect survival (Cox PH) model, to account for shared frailty/correlation for people belonging to the same general practice. However, since air pollution data are estimated at 20mx20m resolution, it seems that there is another level of shared frailty/or clustering (possibly demanding different statistical model, two-level frailyt), of people who are assigned same air pollution levels, which is within general practice area? Or did all subjects have individual air pollution levels assigned? This is not clear completely, and it would be helpful if authors explain this better.

Response: **The clustering by general practice is an inherent and important feature of these large-scale databases, where practice-specific recording patterns and trends can arise, and**

**this should be accounted for where possible. For example, two identical symptomatic patients in two different practices may not both receive identical diagnoses. However, the further clustering the reviewer describes here (spatial, household) would not have the same impact. While it may be true that patients on the same street/household may be more similar than patients on a different street/household from the same practice, we are not convinced this needs to be accounted for in the same way. Nor are we aware of any analysis of large primary care databases that has acknowledged or adjusted for clustering at this level. Finally, we cannot adjust for spatial auto-correlation (which we think the reviewer is describing) because we were not allowed the specific geographical information needed for this; again, because of the requirement to maintain anonymity.**

**To clarify the pollution assignment again: we used the postcode (unseen by us) on the patients' primary care record to assign the pollution exposure. For the air pollution, this had been generated from the mapping of 20m x 20m gridcodes onto the postcode (so more than one postcode could in theory map to a gridcode). So within a practice, patients will be assigned different exposure levels as the practice will cover hundreds (or even thousands) of postcodes**

8. If understood correctly, it seems that road traffic noise data were modeled at poorer resolution (zip codes) than air pollution data (20mx20m)? Could this then explain weaker association with dementia, due to smaller contrast in exposure, which fail to capture finer, real exposure contrasts in noise exposure at residence? If this is understood correctly, it should be acknowledged in the discussion. Another matter is 'clustering' of people with same noise levels, and how this differs from 'air pollution' and primary physician 'cluster'? At the same time, outcome and confoudern data are available at the individual level. The data structure is somewhat complicated and little difficult to follow at times.

Response: **Both the air pollution and noise data were modelled at comparable resolutions. The difference was that for the noise data, the centroids of each postcode were directly used. For the air pollution data, the centroids of each postcode were mapped to nearest 20x20m point of the dispersion model. Postcodes will vary in size geographically, but average about 15 households. So depending on the size of the postcode, it is feasible that more than one could be mapped to the same 20x20m point.**

**In our resulting dataset, we think the key difference between the air and noise pollutants (in terms of geographical mapping) is in the intra-class correlation coefficients calculated by practice (now added to Table 2). These are >0.7 for the air pollutants, but 0.05 for noise. Thus, most of the differences between patients modelled air pollution exposure in our study is between practice, while for modelled noise it is within practice.**

**We have added these estimates to Table 2 now, and updated the results and discussion accordingly.**

9. Please add more detail on the confounder definition in the Methods. Are they collected by GP? BMI is measured or self-reported? In addition, were co-morbidities defined from GP records? Was this done in the same way as in reference 16? On page 6, it is stated that 'Following previous methods', and referring to author's earlier paper: 'we also collated information on ethnicity, smoking, etc..', but it would be nice to have this important information about relevant confounders sources and definition without having to look up earlier paper.

Response: **We were trying to save words here, but accept some detail has been lost. We have now expanded this section a little, and removed this reference. However, we have added another reference that explains the list of co-morbidities we initially considered.**

10. Lack of information on education, income, occupation, IQ, etc., all of which may be important confounders/risk factors of dementia, is a weakness of this study (especially is there is some selection by socio-economic status) which should be acknowledged up front as one of the major weaknesses.

Response: **We accept this is a limitation of any study this size based on routine data, and have acknowledged as such in the discussion. Many of these factors contribute to the Index of Multiple Deprivation, although that is an area-based measure. We cannot discount residual confounding, but note that the association was not explained even when adjusting for co-morbidities on the disease pathway, which would themselves be associated with SES (and indeed risk factors earlier in life such as mid-life obesity).**

11. Page 15, line 37 what is meant by unusual clustering of their address flag?

Response: **This was in relation to "where 4 or more patients aged 65-99 were recorded living at the same address" (methods, page 6, line 25). But we agree it was poorly worded and have simplified this sentence now.**

12. Discussion, page 17, line 24-30, authors refer to study by Oudin et al. but forgot to refer to it. I assume this is referene 37, Oudin et al., pleas einsert it.

Response: **Thank you – we have corrected this now.**

13. Authors failed to mention study by Kioumourtzoglo et al. large study of 9.8 million Medicare enrollees ≥ 65 years in US dwhich etected association between PM2.5 and first-ever hospitalization for dementia (HR = 1.08; 1.05-1.11) and AD (HR = 1.15; 1.11-1.19) per 1 µg/m,3 in line with current findings:

Kioumourtzoglou M-A, Schwartz JD, Weisskopf MG, Melly SJ, Wang Y, Dominici F, et al. 2016. Long-term PM2.5 Exposure and Neurological Hospital Admissions in the Northeastern United States. Environ. Health Perspect. 124:23–9; doi:10.1289/ehp.1408973.

Response: **Thank you for alerting us to this omission and the similar findings. We have added to now and expanded a section of the discussion to include these findings.**

14. Study by Wu et al. is from 2015, and not 2017, as stated in the Reference list.

https://www.ncbi.nlm.nih.gov/pubmed/27239507

Response: **Thank you – we have corrected this now**

**VERSION 2 – REVIEW**

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| **REVIEWER** | Zorana Jovanovic Andersen<br>University of Copenhagen, Denmark |
| **REVIEW RETURNED** | 29-May-2018 |

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| **GENERAL COMMENTS** | I am pleased with authors' answers to mine and other reviewers' comments. |

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| **REVIEWER** | Giulia Cesaroni<br>Department of Epidemiology, Lazio Regional Health Service, Rome, Italy |
| **REVIEW RETURNED** | 11-Jun-2018 |

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| **GENERAL COMMENTS** | I am happy with the revision. |